Serologic correlates of protection from pertussis vaccines

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Lessons from pertussis vaccine trials

Evidence for relative efficacy against less severe disease
Efficacy of vaccines in Italian trial against increasing duration of cough

Greco et al NEJM 1996; 334: 341
Vaccine efficacy in relation to disease severity score
Senegal trial N=834 cases

1. Prezosi Clin Inf Diseases 2003; 37: 772
Swedish vaccine trials

Sweden II - 2,4,6 schedule, poor DTPw
Sweden III – 3,5,12 schedule, good DTPw
Sweden II - Gustafson, NEJM 1996; 334-349

- 3 vaccines
  - Connaught WC
  - Connaught 5C (10µg PT, 3 µg PRN)
  - GSK 2C
  - DT

- Pertussis epidemic during trial period

- Active follow-up:
  - Nurse contacted household every 6-8 weeks and parents asked to report
  - Standard clinical data
  - Nasopharyngeal aspirates
  - Paired serum
1. Case definition = >21 days cough + cult or serology

24336

eligible 14507

9829 (40.4%)

689 paired serum

Follow up 21-24 m N=737 pertussis cases

<table>
<thead>
<tr>
<th></th>
<th>2C</th>
<th>5C</th>
<th>WC</th>
<th>DT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence per 10⁵ post 3 d (culture pos %)</td>
<td>3200 (56%)</td>
<td>1200 (42%)</td>
<td>4000 (59%)</td>
<td>7800 (73%)</td>
</tr>
<tr>
<td>VE 21 d cough (post 3 d) (95% CI)</td>
<td>59% (51-66)</td>
<td>85% (81-88)</td>
<td>48% (37-56)</td>
<td>-</td>
</tr>
<tr>
<td>VE any cough (95% CI)</td>
<td>42% (32-51)</td>
<td>78% (73-82)</td>
<td>41% (30-51)</td>
<td>-</td>
</tr>
</tbody>
</table>
Sweden III Trial – Olin et al Lancet 1997;350;1569

10047 eligible
82864 randomised (82.5%)

72698
3, 5, 12 mths

10194
2, 4, 6 mths

<table>
<thead>
<tr>
<th>Component Type</th>
<th>GSK 2 Component</th>
<th>Chiron 3 Component</th>
<th>Canada 5 Component</th>
<th>UK Whole Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18145</td>
<td>18184</td>
<td>18196</td>
<td>18173</td>
</tr>
<tr>
<td></td>
<td>2552</td>
<td>2544</td>
<td>2551</td>
<td>2547</td>
</tr>
</tbody>
</table>
Vaccine efficacy – Sweden III trial
N = 72655  Follow up period = 22 months
4 pertussis vaccine groups, no DT arm

Outcomes

1. *Culture confirmed*
   - all post dose 3
     - with ≥ 21 days paroxysmal cough
     - with any cough
   - all post dose 1
     - with ≥ 21 days paroxysmal cough
     - all between dose 2 and 3

2. *Not culture confirmed*
   - all parent reported whooping cough parent stated ‘certain’
Pertussis cases by case definition – Sweden III

<table>
<thead>
<tr>
<th></th>
<th>3 Component N= 17679</th>
<th>5 Component N=17686</th>
<th>Whole Cell N=17453</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with cough of any duration (&gt;=21 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 doses</td>
<td>N=49 (21)</td>
<td>N=27 (13)</td>
<td>N=19 (15)</td>
</tr>
<tr>
<td>Incidence of all culture + /10^5 (&gt;= 21 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 doses</td>
<td>155 (67)</td>
<td>85 (50)</td>
<td>61 (48)</td>
</tr>
<tr>
<td>RR (any cough)</td>
<td>2.6 (1.5-4.3)</td>
<td>1.4 (0.8-2.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Incidence of all culture + / 10^5 between dose 2 and 3 (&gt;21 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>353 (210)</td>
<td>152 (95)</td>
<td>181 (67)</td>
</tr>
<tr>
<td>RR 1.0 (2C vaccine)</td>
<td>0.5 (0.4-0.8)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.3 (0.2-0.5)</td>
</tr>
</tbody>
</table>

RR for 3C vs 5C = 1.8 (95% CI 1.1 to 2.9)
Serologic correlates

Household contact studies
Household contact studies post vaccine trials
- Sweden and Germany

- Needed for interpretation:
  - Antibody levels obtained pre-exposure
  - Antibody levels obtained within a short time post exposure

- Challenges:
- Different vaccines
  - different antigenic components
  - different combinations of antibody results
- Limited eligible subjects
  - power to compare outcomes
Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*

Jann Storsaeter*, Hans O. Hallander†, Lennart Gustafsson† and Patrick Olin†

Figure 1  Study children exposed to *B. pertussis* in the household.
Household contact study in Sweden: WHO “typical” pertussis

<table>
<thead>
<tr>
<th>Anti-PT</th>
<th>Fimbriae</th>
<th>69 kDa, pertactin</th>
<th>No. exposed</th>
<th>No. cases</th>
<th>Attack rate, %</th>
<th>Vaccine efficacy, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/L</td>
<td>H</td>
<td>H</td>
<td>49</td>
<td>5</td>
<td>10</td>
<td>85</td>
<td>65–94</td>
</tr>
<tr>
<td>H/L</td>
<td>L</td>
<td>H</td>
<td>6</td>
<td>1</td>
<td>17</td>
<td>75</td>
<td>0–96</td>
</tr>
<tr>
<td>H/L</td>
<td>H</td>
<td>L</td>
<td>16</td>
<td>3</td>
<td>19</td>
<td>72</td>
<td>22–90</td>
</tr>
<tr>
<td>H</td>
<td>L</td>
<td>L</td>
<td>33</td>
<td>12</td>
<td>36</td>
<td>46</td>
<td>14–66</td>
</tr>
<tr>
<td>DTP groups</td>
<td>L</td>
<td>L</td>
<td>40</td>
<td>27</td>
<td>68</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DT group</td>
<td>L</td>
<td>L</td>
<td>65</td>
<td>44</td>
<td>68</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**NOTE.** D, diphtheria; H, high preexposure antibody levels; H/L, antibody levels independent of high or low levels (as defined in text); L, low preexposure antibody levels; P, pertussis; PT, pertussis toxin; T, tetanus. Data from [8].
Household contact study in Sweden: Any cough, laboratory-confirmed

Table 3. Attack rate of *Bordetella pertussis* with ≥1 day of cough and corresponding estimates of vaccine efficacy in Sweden 1 trial household exposure.

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<td>6</td>
<td>4</td>
<td>67</td>
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<td>0–57</td>
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<td>H</td>
<td>L</td>
<td>16</td>
<td>11</td>
<td>69</td>
<td>22</td>
<td>0–44</td>
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<td>L</td>
<td>L</td>
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<td>85</td>
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Low levels of antipertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to *Bordetella pertussis*

Jann Storsaeter*, Hans O. Hallander, Lennart Gustafsson, Patrick Olin

*Swedish Institute for Infectious Disease Control, Solna, Sweden*

### Table 2
Duration of cough in primary cases (study infants) and number of exposed household members by vaccine group and age

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<thead>
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<th>Primary cases among study infants</th>
<th>Exposed household members</th>
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<tbody>
<tr>
<td>Vaccine group</td>
<td>Adults born 1978 or before</td>
</tr>
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</tr>
<tr>
<td>DTPa2</td>
<td>116 (76%)</td>
</tr>
<tr>
<td>DTPa5</td>
<td>34 (77%)</td>
</tr>
<tr>
<td>DTPwc</td>
<td>115 (72%)</td>
</tr>
<tr>
<td>DT</td>
<td>343 (76%)</td>
</tr>
<tr>
<td>All</td>
<td>608 (75%)</td>
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<tr>
<th>Primary cases among study infants</th>
<th>Duration of cough (mean ± S.D.)</th>
<th>Exposed household members</th>
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</thead>
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<tr>
<td>Vaccine group</td>
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<td>Adults born 1978 or before</td>
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<td>DTPa5</td>
<td>46.5 ± 44.0</td>
<td>34 (77%)</td>
</tr>
<tr>
<td>DTPwc</td>
<td>66.5 ± 31.4</td>
<td>115 (72%)</td>
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<td>DT</td>
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Antibody response patterns to pertussis in vaccinated and unvaccinated children

Re-analysis of household contact study data

- **Post pertussis infection:**
  1. PT only vaccine
     - Blunted response to FHA c.f. PT+FHA
  2. PT+FHA vaccine
     - Blunted response to PRN and Fim
  3. DT vaccine
     - Lower responses to all vaccine antigens

Cherry et al Clin and Vaccine Immunol 2010; 17: 741
Conclusions from household contact studies

- There are correlations
- Lack of PT antibody is single most important factor
  - Especially for severe disease
  - PT wanes rapidly post 3 dose infant schedule
  - Correlation with whole cell vaccine efficacy less clear
- Pertactin antibody and Fimbrial antibodies
  - Correlate with agglutinogens
  - Important against less severe disease
- Combinations of antibody have synergistic effects
Serologic correlates – summary

- Agreement on important factors
  - Antibody combinations
    - PT, Pertactin and Fimbriae
  - Case definition

- Uncertainties
  - Thresholds
    - by combination
    - by case definition
  - Case definition and transmission
  - Importance of Fim as independent factor
Re-introduction of pertussis vaccination – the Swedish experience

1. Carlsson and Trollfors Vaccine 2009

Fig. 2. Age-specific incidence of laboratory-confirmed pertussis in Sweden during 10 calendar years before and 11 calendar years after introduction of pertussis vaccination (using aP-containing vaccines) into the general vaccination programme in 1996 (mean incidence rates per 100,000 population 1986–1995 and 1997–2007). An enlarged version of the bar chart for the age groups 10 years and above is shown in the insert [2].
Seroprevalence of pertussis antitoxin (anti-PT) in Sweden before and 10 years after the introduction of a universal childhood pertussis vaccination program

HANS O. HALLANDER; MIKAEL ANDERSSON, LENNART GUSTAFSSON, MARGARETHA LJUNGMAN and EVA NETTERLID
Summary

- Immunity to pertussis is **multifactorial**
- Clearest evidence is for **susceptibility related to low antibody levels**
- **More than one antibody** is important
- **More evidence** on serologic correlates is needed
  - ? Challenge studies

**Hypothesis: Hierachy of immunity**
- Post symptomatic infection
- Whole cell vaccines: highest vs lowest efficacy
- Acellular vaccines: more vs less components